IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

RAVGEN, INC., **Plaintiff,** **v.** **NATERA, INC. AND NSTX, INC.,** **Defendants.**	**Civil Action No. 1:20-cv-00692-ADA** **JURY TRIAL DEMANDED**

PLAINTIFF RAVGEN, INC.'S OPENING CLAIM CONSTRUCTION BRIEF

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INTRODUCTION

This patent infringement action involves technology for the preparation and/or analysis of "free" nucleic acids, including in non-invasive prenatal testing as well as cancer and organ transplant-related applications. Plaintiff Ravgen, Inc. ("Ravgen") owns fundamental patents relating to that technology, including U.S. Patent Nos. 7,332,277 ("the '277 Patent") and 7,727,720 ("the '720 Patent") (collectively, the "Patents-in-Suit"). Natera, Inc. and NSTX, Inc. (collectively, "Defendants") commercialize genetic tests using free DNA that include the patented methods.

As discussed below, Ravgen proposes that the disputed claim terms be given their plain and ordinary meaning in the art, as supported by the intrinsic record. By contrast, Defendants repeatedly seek to depart from those ordinary meanings and the guidance in the intrinsic record, asking the Court to rewrite the claims to add extraneous limitations. Because Defendants' theories violate fundamental principles of claim construction, they should be rejected.

BACKGROUND

The Patents-in-Suit relate to the preparation and/or analysis of "free" nucleic acids (*e.g.*, DNA) circulating in bodily fluids, such as blood. Although the vast majority of human DNA in blood is contained within the cells, the plasma (the liquid portion of blood) may also contain "cell-free" or "free" DNA circulating outside the cells. Grody Decl.[1] ¶ 18. For example, the plasma portion of a pregnant female's blood includes circulating free fetal DNA, and that portion of a cancer patient's blood may include circulating free tumor DNA. *Id.*

Prior to the inventions of the Patents-in-Suit, there was a need for non-invasive genetic testing techniques utilizing such free DNA. *Id.* at ¶ 19. However, at that time, the use of such free DNA for genetic testing was limited by the low percentage of free fetal (or other circulating)

[1] "Grody Decl." refers to the December 14, 2020 Declaration of Wayne W. Grody, M.D., Ph.D., filed herewith.

DNA that could be recovered from a sample using existing techniques. *Id.*; *see* '277 Patent at 32:24–39; '720 Patent at 33:31–46. The inventor of the Patents-in-Suit, Dr. Ravinder S. Dhallan, hypothesized that the cause of that low recovery using existing methods was lysis of maternal cells (*i.e.*, the rupture of cell membranes) during sample collection and preparation, resulting in the release of DNA from maternal blood cells into the plasma and dilution of the free fetal DNA.

Dr. Dhallan developed novel methods of preparing and analyzing free nucleic acids that included adding to the sample an agent that would inhibit lysis of any cells present in the sample. The addition of this agent would reduce the release of DNA from any cells present in the sample (*e.g.*, maternal blood cells), thereby increasing the percentage of free circulating DNA (*e.g.*, free fetal DNA) recovered as compared to prior methods that did not involve adding such agents.

> The addition of cell lysis inhibitors, cell membrane stabilizers or cross-linkers to the maternal blood sample can increase the relative percentage of fetal DNA. While lysis of both maternal and fetal cells is inhibited, the vast majority of cells are maternal, and thus by reducing the lysis of maternal cells, there is a relative increase in the percentage of free fetal DNA.

'277 Patent at 32:33–39; '720 Patent at 33:39–45; *see also* Ex. 3 at -00012668–69. Although substances such as membrane stabilizers, cross-linkers, and/or cell lysis inhibitors were known in the art for preventing cell lysis in other contexts—*e.g.*, preserving cells for analysis—use of those agents in preparing and analyzing ***free*** nucleic acids, as claimed in the Patents-in-Suit, was novel. *See id.* at -00012671; Ex. 4 at -00013025–29; Ex. 5 at -00015534–38; Grody Decl. ¶¶ 20–21.

The '277 Patent also addresses the challenge of distinguishing between the free maternal and fetal DNA in a sample to detect fetal chromosomal abnormalities. Dr. Dhallan developed a novel method (claimed in the '277 Patent) for such detection that involves sequencing only discrete positions (or loci) on chromosomes in a mixture of free fetal and free maternal DNA and does not require physically separating the fetal DNA from the maternal. '277 Patent at 34:63–35:37; Grody

Decl. ¶¶ 24–25. That method involves identifying a locus that is heterozygous (meaning multiple different nucleotide sequences, "alleles," are present at the locus) in that mixture of free maternal and fetal DNA and quantitating the ratio of the amount of each different allele at that locus to determine the presence or absence of a fetal chromosomal abnormality. *Id*. at ¶¶ 22–28.

DISPUTED TERMS

I. "relative amount of [the] alleles" ('277 Patent, Claims 1, 116)

Ravgen's Proposed Construction	Defendants' Proposed Construction
plain and ordinary meaning	proportions of alleles based on comparisons between amounts of fetal and maternal DNA

Defendants do not contend that the term "relative amount of [the] alleles" is expressly defined in the specification nor that patentee made any statements of clear disavowal limiting its scope; thus, the term should be given its plain and ordinary meaning. *See Thorner v. Sony Comput. Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). Defendants' construction improperly deviates from that plain meaning by importing an extraneous limitation—that the proportions of alleles be "based on comparisons between amounts of fetal and maternal DNA"—that is untethered to the claim language and injects unnecessary ambiguity into the otherwise clear claim language.

A. Because The Plain Language Is Clear, This Term Requires No Construction.

The plain meaning of this claim term is clear in the context of the claims in which it appears and therefore needs no construction. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). For example, Claim 1 of the '277 Patent requires "quantitating the ratio of the ***relative amount of alleles*** at a heterozygous locus of interest in a mixture of template DNA."[2] *See also id.* at Claim 116. By definition, at least two distinct alleles, *e.g.*, allele 1 and allele 2, are present at any heterozygous locus of interest. *See id.* at 29:11–32. Thus, in the context of the

[2] Emphasis has been added unless otherwise noted.

claims, the "ratio of the relative amount of [the] alleles at a heterozygous locus of interest" is the ratio of the amount of one allele relative to the amount of each other allele at that locus.

The specification further illustrates the straightforward application of this term according to its plain and ordinary meaning. In Example 14, the amount of each allele present at each heterozygous locus of interest in a mixture of DNA from a mother and her child was measured. '277 Patent at 211:32–36, 212:27–36. Then, "[t]he ratio at each heterozygous SNP was calculated by dividing ***the value obtained for allele 1 by the value obtained for allele 2***." *Id.* at 216:3–5; *see id.* 216:5–8. That example thus confirms that the claimed "relative amount of the alleles" refers to the comparative amounts of each distinct allele present at the heterozygous locus.

B. Defendants' Proposed Construction Improperly Imports An Extraneous Limitation And Injects Ambiguity Into The Clear Claim Language.

Defendants' proposal imports a new requirement that is untethered to the plain language of "relative amount of alleles" and, as shown below in context, renders the claims indecipherable:

> quantitating a ratio of **the proportions of alleles based on comparisons between amounts of fetal and maternal DNA** at a heterozygous locus of interest in a mixture of template DNA, wherein said mixture comprises maternal DNA and fetal DNA . . .

'277 Patent, Claim 1. Defendants assert that the word "relative" in this claim term indicates that the "proportions of alleles" in the heterozygous mixture must be compared to something else. *See* Ex. 6 at 1. But that theory finds no support in the claims. Rather, in the context of the claims ("ratio of the ***relative*** amount of [the] alleles"), "relative" modifies "amount of alleles," indicating that the claimed ratio compares the amounts of different alleles relative to each other. "Relative" does not modify "ratio," and the claims do not require that the allelic ratio be compared any other quantity, let alone "comparisons between amounts of fetal and maternal DNA."[3] Further,

[3] Nor do the extrinsic dictionary definitions of "relative" identified by Defendants warrant departing from the plain meaning. First, because the plain meaning of that word is clear on its

Defendants' proposal improperly injects new sources of ambiguity and dispute into the clear claim language, for example, as to the meaning of "comparisons between amounts of fetal and maternal DNA"; how said fetal and maternal DNA should be measured; and how said comparisons are to be used as a basis to determine the "proportions of alleles." *See Oil States Energy Servs., L.L.C. v. Trojan Wellhead Prot., Inc.*, No. 6:12-CV-611, 2014 WL 12360946, at *8 (E.D. Tex. June 23, 2014) (rejecting proposed construction that introduced an "unnecessary and ambiguous term").

To the extent that Defendants' construction requires comparison of the ratio of the measured amounts of alleles at the heterozygous locus of interest and some previously calculated expected ratio based on "the amounts of fetal and maternal DNA" in the sample, that construction improperly imports a limitation from the specification. While the specification describes examples comparing actual ratios of the amounts of alleles present at a locus of interest to expected ratios of alleles at that locus, derived from, for example, a population norm or a comparison to a control chromosome in the sample, those comparisons are not required by the claims. *Compare* '277 Patent at 234:36–38, 212:33–36 *with id.* at Claims 1, 116. Thus, to the extent it is understandable, Defendants' proposed construction improperly imports a limitation from the specification. *Cloud Farm Assocs. LP v. Volkswagen Grp. of Am., Inc.*, 674 F. App'x 1000, 1007 (Fed. Cir. 2017).

II. "sample" ('277 Patent, Claims 1, 55, 81, 116; '720 Patent, Claim 1)

Ravgen's Proposed Construction	Defendants' Proposed Construction
plain and ordinary meaning	a representative specimen taken for scientific testing

The parties appear to agree that the term "sample" should be construed according to its

face, the Court need not consider extrinsic evidence. *Phillips*, 415 F.3d at 1317–19. Moreover, the proffered definitions, which merely confirm that the word "relative" indicates a relationship (as opposed to an absolute), are consistent with the plain meaning of "relative" in the claims to describe the relationship between the amounts of different alleles. *See* Ex. 7 at -001859; Ex. 8 at -001885; Ex. 9 at -001899.

plain and ordinary meaning. Because "there is nothing about the claim term ['sample'] that is confusing[,] . . . the term requires no construction." *Pisony v. Commando Constr., Inc.*, No. 17-cv-00055-ADA, 2019 WL 928406, at *5 (W.D. Tex. Jan. 23, 2019).[4] Yet Defendants' proposed construction unjustifiably replaces the easily understood term "sample" with "specimen" and imposes two new unsupported limitations: "representative" and "taken for scientific testing."

The ordinary meaning of "sample" to a person of ordinary skill in the art ("POSITA") does not require that it be "representative" or "taken for scientific testing"; nor does the intrinsic record support those requirements. Consistent with that plain meaning, the specification and file histories impose no requirement that a "sample" be "representative." The specifications use "sample" broadly to describe many sample types, including blood samples containing free nucleic acid, without requiring that those samples be representative. *See, e.g.*, '277 Patent at 6:41–51; '720 Patent at 6:16–25. And that other elements of the claimed methods may involve scientific testing of the claimed sample, *see, e.g.*, '277 Patent at 469:12–17; '720 Patent at 535:21, does not support altering the ordinary meaning of "sample" to ***require*** that it be "taken for scientific testing."

The only technical dictionary Defendants identify does not include an entry for "sample," confirming that "sample" is not a technical term requiring clarification for the jury. *See* Ex. 10 at -001872. And Defendants' proposed construction does not appear in any of the non-technical dictionary definitions they proffer. *See* Ex. 7 at -001860; Ex. 10 at '72; Ex. 8 at -001886; Ex. 9 at -001900. Although one such dictionary defines the noun "sample" as a "specimen," substitution of the non-technical term "sample" with a synonym "specimen" will not assist the jury and is thus unwarranted. *See C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862–63 (Fed. Cir. 2004).

[4] Moreover, the parties do not appear to dispute the scope of the term as it applies to infringement and validity issues in this case. For example, the parties appear to agree that this term does not exclude samples to which an exogenous agent has been added. Ex. 6 at 2.

III. "determining the sequence [of alleles] [at the/of a] locus of interest" ('277 Patent, Claims 1, 116, 55)[5]

Ravgen's Proposed Construction	Defendants' Proposed Construction
plain and ordinary meaning	ascertaining the identity of one nucleotide or nucleoside or of contiguous nucleotides or nucleosides of [an allele/a nucleic acid] at a selected region of nucleic acid that is within a larger region of nucleic acid

The determining limitation uses clear language according to its plain and ordinary meaning in the art; thus, no construction is necessary. Defendants' proposed construction rewrites that easily understandable claim limitation to replace the words chosen by the patentee with Defendants' own unsupported and convoluted language. The Court should reject that proposal.

A. Defendants' Attempt To Replace "Determining" With "Ascertaining" Finds No Support In The Record.

Defendants' proposed replacement of the patentee's chosen word—"determining"—with Defendants' preferred term—"ascertaining"—is unsupported by the intrinsic record and unnecessary here. Because the patentee did not define the term "determining" nor disavow any of its scope, no deviation from its ordinary meaning is justified.[6] *See Thorner,* 669 F.3d at 1365. Although the alleged basis for that proposed swap is that "ascertaining" and "determining" are "synonyms," the record lacks support for that assertion. The word "ascertaining" does not appear in the patent; nor have Defendants identified extrinsic evidence that supports that definition. Moreover, "determining" is not a technical term requiring clarification; thus, substitution with Defendants' proposed "synonym" is unwarranted. *See C.R. Bard,* 388 F.3d at 862–63.

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[5] Claims 1 and 116 (but not Claim 55) include the phrase "of alleles," which Defendants propose replacing with "of an allele." Otherwise, Defendants propose the same construction for all three versions of the term, which are collectively referred to herein as the "determining limitation."

[6] To the contrary, the section in the specification entitled "Method for Determining the Sequence of a Locus of Interest" discloses that "***[a]ny method*** that provides information on the sequence of a nucleic acid can be used." '277 Patent at 36:4–22; *see also id.* at 6:26–34, 8:62–9:7.

B. Defendants' Insertions Of Purported Lexicographic Definitions Unjustifiably Deviate From The Specifications And Are Inconsistent With The Claims.

Although Defendants allegedly base their proposed construction on disclosures in the specification defining the terms "sequence" and "locus of interest," Defendants' proposed construction deviates from those purported definitions,[7] improperly imposing limitations that are inconsistent with the claim language and insert ambiguity for a jury. For example, Defendants alter the purported definition of "sequence" by inserting the technical term "nucleoside(s)." Defendants assert that this proposed modification is necessary to encompass RNA sequences (which contain nucleosides) as well as DNA sequences. Ex. 6 at 1. But the asserted claims in which the determining limitation appears all recite DNA, rendering Defendants' insertion unnecessary and inconsistent with its context in the claims. *See Phillips*, 415 F.3d at 1314.

Additionally, as shown below in Claim 1, Defendants' proposed construction: (i) severs the connection between "**the** locus of interest" in this limitation and its antecedent basis; and (ii) ignores the plural "**alleles**" instead requiring determining the sequence of only "**an** allele."[8]

'277 Patent Claim 1	Claim Language With Defendants' Proposed Construction
"[A] heterozygous locus of interest in a mixture of maternal and template DNA . . . wherein said heterozygous locus of interest has been identified by determining the sequence of **alleles** at **the** locus of interest[.]"	"[A] heterozygous locus of interest in a mixture of maternal and template DNA . . . wherein said heterozygous locus of interest has been identified by ascertaining the identity of one nucleotide or nucleoside or of contiguous nucleotides or nucleosides of **an allele** of a nucleic acid at **a** selected region of nucleic acid that is within a larger region of nucleic ac*id.*"

As shown, that claim requires that the earlier-recited ***heterozygous*** locus of interest has

[7] The specification explains that, consistent with the plain and ordinary meaning of those terms, "sequence means the identity of one nucleotide or more than one contiguous ***nucleotides*** in a polynucleotide," '277 Patent at 29:33–37; and "[b]y a 'locus of interest' is intended a selected region of nucleic acid that is within a larger region of nucleic acid," *id.* at 29:6–7.

[8] Defendants proffer no basis for these alterations. In fact, they stated that the swap of "**an** allele" for "allele**s**" and the removal of the antecedent basis of "**the** locus of interest" were likely unintentional. Ex. 6 at 1–2. But Defendants did not modify their proposal to address those issues.

been identified by "determining the sequence of allele**s** at **the** locus of interest." Thus, the patentee's chosen language makes clear that "at **the** locus of interest" in this limitation refers to **the** heterozygous locus of interest referenced earlier in the claim. Yet Defendants' construction (*e.g.*, "at **a** selected region") eliminates that requirement. Further confusing matters, Defendants seek to selectively incorporate patentee's purported lexicographic definition of the phrase "locus of interest" only in the determining limitation, while leaving that phrase undefined elsewhere in Claims 1 and 116. Thus, far from clarifying the claim language, Defendants' proposal provides the jury with multiple alternative phrasings for "locus of interest" within the same claim as well as severing patentee's use of antecedent basis with respect to that term. And Defendants' proposed replacement of the plural "allele**s**" with the singular "**an** allele" is also inconsistent with the claim language. Because multiple alleles (different sequences) are present at a heterozygous locus by definition, identifying such a locus by "determining the sequence of alleles at the locus" as claimed involves determining the sequence of more than one allele. *See* '277 Patent at 29:26–28.

Thus, Defendants' proposal unjustifiably alters the patentee's chosen language, rendering the determining limitation incompatible with its context in the claims, and should be rejected.

IV. "agent that [inhibits cell lysis to inhibit the lysis of cells/inhibits lysis of cells/impedes cell lysis] . . . wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor" ('277 Patent, Claims 8, 55, 81; '720 Patent, Claim 1)

Ravgen's Proposed Construction	Defendants' Proposed Construction
plain and ordinary meaning In the alternative, plain and ordinary meaning, wherein the plain and ordinary meaning is: "a substance that inhibits the rupture of cells that is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor, and does not include other categories of substances that only indirectly affect cell lysis such as anticoagulants and chelators like EDTA, nor endogenous substances that are not selected to be added"	Compound that slows or stops cell lysis, including anticoagulants like EDTA (clarification of/consistent with plain and ordinary meaning). In the alternative, indefinite.

The parties do not dispute that the agent limitation[9] should be construed according to its plain and ordinary meaning. Defendants attempt to depart from that clear ordinary meaning to encompass anticoagulants like EDTA and even naturally-occurring (endogenous) substances in a sample and argue in the alternative that the claim limitation is indefinite. Those theories ignore the clear boundaries defined by the claims and conflict with the intrinsic record.

A. The Intrinsic Record Confirms That A POSITA Would Have Readily Understood The Plain And Ordinary Meaning Of The Agent Limitation.

As explained by Dr. Wayne W. Grody, a professor of Medical Genetics and Molecular Diagnostics at UCLA School of Medicine with decades of experience in the field, a POSITA would have readily understood the scope of the agent limitation based on the plain language. Grody Decl. ¶ 30. That language delineates clear requirements that the claimed agent: (1) include a particular functional capability ("agent that [inhibits lysis of cells], if cells are present");[10] and (2) be selected from well-defined categories of substances ("wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor"). *Id.* at ¶¶ 31, 35. The intrinsic record confirms that the Patents-in-Suit use that claim language according to its plain meaning in the art and provides extensive guidance informing a POSITA of the limitation's scope.

First, the intrinsic record confirms that the plain language of the limitation requires that the claimed agent be capable of inhibiting cell lysis, if cells are present. As Dr. Grody explains, the specifications use the term cell lysis consistently with its plain and ordinary meaning in the art, *i.e.*, the rupture of the cell membranes resulting in the release of the cells' contents, which include

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[9] The phrases "inhibits cell lysis to inhibit the lysis of cells," "inhibits lysis of cells," and "impedes cell lysis" are used synonymously in the claims and the intrinsic record, and Defendants have confirmed that no dispute exists based on purported differences between those phrases. Ex. 6 at 2. Therefore, "impedes"/"inhibits" and "cell lysis"/"lysis of cells" are used interchangeably herein, and "agent limitation" is used herein to refer to all versions of this claim term.

[10] Defendants remove "if cells are present" from this claim term, but as explained in Section V where it is addressed separately, that phrase meaningfully clarifies the agent limitation.

cellular DNA. Grody Decl. ¶¶ 31–32; Ex. 11 at -00001366. The specifications further elucidate the functional capability of the claimed agent—to reduce or prevent lysis of cells, if present—including by describing experiments using exemplary agents for that purpose. For example, Examples 4 and 15 demonstrate that by adding such agents to maternal blood samples, "an overall increase in [the percentage of] fetal DNA was achieved by ***reducing the maternal cell lysis***, and thus, reducing the amount of maternal DNA present in the sample." '277 Patent at 91:44–46; *see id.* at 223:1–2 ("The effect of ***stabilizing cell membranes and reducing the release of free DNA*** was not limited to formalin."); '720 Patent at 92:10–12, 213:44–45; Grody Decl. ¶¶ 33–34.

Second, the intrinsic record confirms that substances in the claimed categories from which the agent is selected—membrane stabilizer, cross-linker, and cell lysis inhibitor—were well known in the art and provides guidance regarding the bounds of each category. For example, the specifications disclose lists of exemplary membrane stabilizers, cross-linkers, and cell lysis inhibitors known in the art. *See, e.g.*, '277 Patent at 31:57–32:21, 226:27–230:21; '720 Patent at 31:43–54, 33:12–28, 216:15–16; Grody Declaration ¶¶ 36–42. And certain dependent claims likewise identify particular substances encompassed by those categories. *See, e.g.*, '277 Patent, Claims 90–93, 132, 133. Additionally, during prosecution, the examiner and the patentee differentiated between prior art compositions covered by the agent limitation (but used in other contexts) and prior art compositions that were not. *See, e.g.,* Ex. 3 at -00012671; Ex. 4 at -00013025–29; Ex. 5 at -00015534–38; Grody Decl. ¶¶ 44, 56–58. As Dr. Grody testifies, a POSITA would have readily understood each of the terms membrane stabilizer, cross-linker, and cell lysis inhibitor to encompass a well-defined category of substances, and the intrinsic record would have confirmed to a POSITA that the Patents-in-Suit use each of those terms according to its ordinary meaning in the art. *Id.* ¶¶ 35–49.

Therefore, based on the claim language and the guidance in the intrinsic record, a POSITA would understand the scope of the agent limitation with reasonable certainty. *Id.* ¶ 29.

B. Defendants' Improper Rewrite Of The Claim Language To Include Anticoagulants Like EDTA And Endogenous Substances Is Inconsistent With The Intrinsic Record And Does Not Render The Agent Limitation Indefinite.

Defendants seek to broaden the scope of the agent limitation to encompass anticoagulants and chelators like EDTA as well as endogenous substances in a sample. Defendants' proposed construction ignores the boundaries expressly defined by the claim language, including by eliminating the requirement that the claimed agent be "selected" from three well-defined categories of substances that do not include anticoagulants and chelators ("membrane stabilizer, cross-linker, and cell lysis inhibitor"). Defendants' attempt to read that limitation out of the claim should be rejected. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006).

1. A POSITA Would Understand The Plain Meaning Of The Agent Limitation To Exclude Anticoagulants And Chelators Like EDTA.

Defendants' proposed construction makes explicit its purpose in broadening the scope of the agent limitation to encompass any compound that even indirectly slows cell lysis, regardless of whether it is a membrane stabilizer, cross-linker, and/or cell lysis inhibitor: to capture "anticoagulants like EDTA." Defendants' theory hinges on the erroneous assumption that because certain extrinsic publications purportedly found that blood clotting may have the side effect of increasing cell lysis, a POSITA would have understood EDTA and other anticoagulants that prevent clotting to meet the agent limitation. But the intrinsic record contradicts that assumption. Instead, it confirms that, according to their plain meanings, the claimed categories—membrane stabilizer, cross-linker, and cell lysis inhibitor—do ***not*** include chelators and anticoagulants like EDTA. Thus, Defendants' theories should be rejected. *See Key Pharms. v. Hercon Labs. Corp.*,

161 F.3d 709, 716 (Fed. Cir. 1998) ("[I]f the meaning . . . is clear from the intrinsic evidence . . . it cannot be altered or superseded by witness testimony or other external sources.").

As Dr. Grody explains, a POSITA would have readily understood that unlike cell lysis inhibitors, which protect and/or preserve the integrity of cell membranes thereby reducing their rupture, anticoagulants like EDTA perform an entirely different function—preventing blood clotting—using a different mechanism—chelating calcium or magnesium. Grody Decl. ¶ 52. Nor would a POSITA interpret either of the terms membrane stabilizer or cross-linker to include anticoagulants or chelators. *Id.* Thus, even if, as Defendants allege, blood clotting may indirectly result in the lysis of cells, a POSITA would have understood the scope of the claimed categories of substances to exclude EDTA and other anticoagulants and chelators. *Id.* ¶ 59.

The explicit guidance in the specification and prosecution history, which distinguishes anticoagulants and chelators like EDTA, confirms that plain meaning of the agent limitation. *Id.* ¶¶ 53–58. Indeed, during prosecution, the patentee explained that EDTA is not a cell lysis inhibitor because "EDTA is a well-known ***chelator of calcium and magnesium***. EDTA is routinely added to blood during the blood collection process as an ***anticoagulant*** due to its ability to chelate calcium." Ex. 3 at -00012670. In fact, as the patentee noted, "EDTA is sometimes included as an ingredient in cell ***lysis*** buffers." *Id.*; Grody Decl. ¶¶ 51, 57. Further, as the patentee pointed out during prosecution, the specifications make clear that EDTA and other anticoagulants and chelators are not cell lysis inhibitors: "EDTA is clearly referred to as a chelator in Applicant's specification, ***not as a cell lysis inhibitor***[,] whereas multiple examples of agents that inhibit cell lysis are provided separately[.]" Ex. 3 at -00012670; *compare* '277 Patent at 31:52–54 *with id.* at 31:57–32:21; *compare* '720 Patent at 32:61–63 *with id.* at 31:43–54; *see* Grody Decl. ¶¶ 56–58.

Additionally, as explained during prosecution, Example 4 of the Patents-in-Suit uses

samples treated with EDTA alone as a control for comparison against samples treated with EDTA ***and formalin*** (the cell lysis inhibitor being evaluated) in order to determine the effect of ***formalin*** on cell lysis. *See* Ex. 3 at -00012670; '277 Patent at 89:1–91:60; '720 Patent at 89:25–92:26; Grody Decl. ¶¶ 54, 58. That example confirms that EDTA is not considered a cell lysis inhibitor: "the percent of fetal DNA in plasma obtained from a pregnant female was determined both in the ***absence*** [*i.e.*, the control tubes containing only EDTA] and presence [*i.e.*, the tubes containing EDTA and formalin] ***of inhibitors of cell lysis***." '277 Patent at 89:11–13; '720 Patent at 89:35–37; *see* Grody Decl. ¶ 54. The patentee explained that, as expected, cell lysis was greatly reduced in the samples to which both EDTA and formalin had been added in comparison to the control samples to which only EDTA had been added, confirming that "formalin and EDTA have very different properties and cannot be equated to each other." Ex. 3 at -00012670. The patentee also identified Example 15, which included EDTA in the samples treated with formalin (a cell lysis inhibitor) in examining "[t]he effect of ***formalin*** on sixty-nine (69) maternal samples." *Id.* at -00012669; '277 Patent at 219:45–46; *see id.* at 219:38–229:22; '720 Patent at 212:66–67, 210:17–218:55; Grody Decl. ¶ 54. Those examples did not evaluate—or even contemplate—EDTA as a potential cell lysis inhibitor. *See* Ex. 3 at -00012670; Grody Decl. ¶¶ 54–58.

The patentee thus distinguished the use of EDTA in the prior art by explaining that the plain meaning of "cell lysis inhibitor" excludes EDTA and other anticoagulants and chelators, and identifying explicit disclosures in the specifications confirming that a POSITA would understand that plain meaning. Defendants' argument that the agent limitation either encompasses anticoagulants like EDTA or is indefinite is therefore meritless in view of the intrinsic record.

2. A POSITA Would Understand The Plain Meaning Of The Agent Limitation To Exclude Endogenous Substances In A Sample.

Defendants also contend—based on their improper construction of the agent limitation—

that the presence of endogenous substances naturally occurring in a sample may suffice to meet that limitation. According to Defendants, because certain substances listed as exemplary membrane stabilizers in the specification, like cholesterol, occur naturally in human blood, ***any*** human blood sample ***necessarily*** meets the agent limitation. That tortured reading eviscerates the agent limitation and conflicts with the plain language and intrinsic record, which inform a POSITA that the claimed agent is a substance that "is selected" for addition to a sample.

The plain language of the agent limitation requires that the sample comprises (or is mixed with) an agent, "wherein said agent ***is selected*** from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor."[11] A POSITA reading that language would understand that the claimed agent must therefore be selected for addition to the sample. Grody Decl. ¶¶ 61–62. As Dr. Grody explains, a POSITA would understand that certain substances that are endogenous to blood (*e.g.*, cholesterol) are also available exogenously and could therefore be ***selected*** as a membrane stabilizer and added to the sample. *Id.* at ¶ 63. But a POSITA would not understand the natural occurrence of an endogenous substance in a blood sample to be a membrane stabilizer, cross-linker, or cell lysis inhibitor that "is selected" as the claimed agent. *Id.*

The intrinsic record confirms that the claimed invention is directed to "[t]he ***addition*** of cell lysis inhibitors, cell membrane stabilizers or cross-linkers to the maternal blood sample" in

[11] In fact, '277 Patent, Claim 8 requires that the "sample ***is mixed with an agent*** . . ." confirming the agent must be added to the sample. Defendants have confirmed that the various phrasings of the agent limitation in the claims are interchangeable. Ex. 6 at 2. However, to the extent that Defendants contend that "sample comprises an agent" should be interpreted differently, the prosecution histories demonstrate that that language merely clarifies that the addition of the claimed agent to the sample is a condition rather than a method step. *See* Ex. 4 at -00013001, -00013005 (amending "agent that inhibits [cell lysis/lysis of cells] has been added to [said/the] sample" in as-issued Claims 55, 81 to "sample comprises . . . an agent that inhibits . . ." in response to examiner remarks that "has been added" should be "is added"); Ex. 5 at -00015525 ('720 Patent, Claim 1 similarly amended). Those amendments do not alter the meaning of the claimed agent to encompass substances endogenous to the sample.

order to reduce the lysis of maternal cells thereby increasing the relative percentage of free fetal DNA relative to samples to which such an agent has not been added. '277 Patent at 32:33–35; Ex. 3 at -00012668 ("[T]he ***addition*** of a cell lysis inhibitor during the [blood] sample preparation process significantly and unexpectedly increase[d] the proportion of fetal DNA."); *see* Grody Decl. ¶¶ 64–66. Indeed, the specifications consistently describe the claimed agent as a substance that is selected and added to a sample. *See, e.g.*, '277 Patent at 6:51–55, 10:11–16, 11:50–53, 12:17–21, 15:58–59, 30:33–32:21; '720 Patent at 6:32–33, 10:30–34, 28:8–12. Further, Example 4 compares blood samples to which the claimed agent (*e.g.*, formalin) has been added to control blood samples to which that agent had not been added, clearly demonstrating to a POSITA that the presence of substances naturally occurring in blood is not encompassed by the agent limitation. '277 Patent at 89:1–91:60; '720 Patent at 89:25–92:26; Grody Decl. ¶ 64.

V. "if cells are present" ('277 Patent, Claims 8, 55, 81; '720 Patent, Claim 1)

Ravgen's Proposed Construction	Defendants' Proposed Construction
plain and ordinary meaning In the alternative, plain and ordinary meaning, wherein according to the plain and ordinary meaning, "if cells are present" conditions the phrases "[inhibits cell lysis to inhibit the lysis of cells/inhibits lysis of cells/impedes cell lysis]."[12]	Conditions the "agent that inhibits lysis of cells" element (clarification of/consistent with plain and ordinary meaning). In the alternative, indefinite.

In the context of the claims, the plain meaning of the "if cells are present" term is clear—it clarifies that the "agent that [inhibits cell lysis]" only need carry out that function if cells are present in the sample. Ignoring that clear meaning, Defendants seek to gut the claims by removing the agent limitation in its entirety in certain contexts (if cells are not present). But Defendants' contrived reading is inconsistent with the claims and intrinsic record and should be rejected.

[12] No dispute exists that these phrases are used synonymously. In Ravgen's alternative proposed construction of the agent limitation, "if cells are present" conditions: "inhibits the rupture of cells."

A. The Plain Language Of The Claims Confirms That The "If Cells Are Present" Term Conditions The Function Of The Claimed Agent.

The context of the phrase "if cells are present" is illustrated below in exemplary Claim 55 of the '277 Patent:

> wherein said sample comprises free fetal DNA and an agent that ***inhibits lysis of cells***, if cells are present, wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor

That context makes clear that "if cells are present" modifies the functional description of the claimed agent—that it inhibits the lysis of any cells that are present. Grody Decl. ¶ 71. That is, "if cells are present" clarifies that the agent need not inhibit cell lysis if no cells are present. *Id.*

The plain language of the claim is inconsistent with Defendants' proposal that the "if cells are present" term instead conditions "wherein said sample [is mixed with/comprises] an agent . . ." such that if cells are not present, no agent is required by the claims. Indeed, if that were the patentee's intent, it could have been expressly written in the claims (*e.g.*, "wherein, if cells are present, said sample [is mixed with/comprises] an agent . . ."). That the claims instead position the phrase "if ***cells*** are present" immediately following the description that the claimed agent inhibits ***cell*** lysis supports the natural reading that the agent need not inhibit cell lysis if no cells are present. Moreover, if the "if cells are present" term were read, as Defendants contend, to condition the entirety of the "sample [is mixed with/comprises] an agent" clauses, then Claim 55 would only require that the "sample comprise[] free fetal DNA" if cells are present. The Court need not adopt that absurd result where a clear meaning can be gleaned from the plain language—*i.e.*, the claimed agent need only inhibit cell lysis when cells are present.

B. The Intrinsic Record Likewise Confirms That The "If Cells Are Present" Term Conditions The Function Of The Claimed Agent.

The intrinsic record confirms that the claims at issue require the inclusion of the claimed

agent regardless of whether cells are present in a sample. For example, the specifications use the phrases "inhibit cell lysis, if cells are present" and "inhibit the lysis of ***cells, if present***" interchangeably to describe the function of the claimed agent, not as a condition for whether or not to include the claimed agent in a sample. *Compare, e.g.*, '277 Patent at 6:51–55, 10:11–16, 15:15–20 *with id.* at 12:17–21, 12:29–33, 12:55–58; *see* Grody Decl. ¶ 73. Additionally, during prosecution, both the examiner and the patentee treated the claims as requiring the addition of the claimed agent regardless of whether cells are present in the sample. For example, the examiner combined the "Umansky" reference with the "Kiessling" reference because Umansky "d[id] not teach ***adding an agent*** that inhibits cell lysis to their maternal ***urine*** samples"—samples that would generally be expected to contain few, if any, cells. Ex. 12 at -00012897, -00012890, 00012896, -00012900; *see also* Ex. 4 at -00013027–28 (patentee response likewise treating claims as requiring the addition of the claimed agent regardless of whether cells are present); Grody Decl. ¶ 74.

Therefore, the Court should reject Defendants' theories and adopt the plain and ordinary meaning of "if cells are present," as Ravgen proposes.

VI. "free fetal DNA isolated" / "isolating free fetal nucleic acid" / "isolating free nucleic acid" ('277 Patent, Claims 55, 81; '720 Claim 1)[13]

Ravgen's Proposed Construction	Defendants' Proposed Construction
plain and ordinary meaning	"free fetal DNA whose proportion versus maternal DNA was increased" / "increasing the proportion of free fetal versus maternal nucleic acid obtained" / "increasing the proportion of free nucleic acid obtained"

Defendants' proposed constructions unjustifiably deviate from the plain and ordinary meaning of the isolating terms to import Defendants' characterization of the benefit of the invention as a whole. Neither the intrinsic nor extrinsic record supports limiting the isolating terms

[13] These terms are referred to collectively herein as "the isolating terms."

as Defendants propose. Moreover, the intrinsic record demonstrates that Defendants' interpretation of the benefit of the invention is fundamentally incorrect. Defendants' proposal should thus be rejected, and the isolating terms given their plain and ordinary meaning.

A. Defendants' Proposed Constructions Unjustifiably Deviate From The Plain And Ordinary Meaning Of The Isolating Terms.

The Patents-in-Suit do not explicitly define the isolating terms. And for an obvious reason: a POSITA would understand that the plain meaning of isolating nucleic acids encompasses standard techniques in the art to remove or reduce other components in a nucleic acid sample. '277 Patent at 31:48–51 ("Any standard DNA isolation technique can be used to isolate" free nucleic acid from a sample.); *see also id* at 26:44–57; '720 Patent at 32:57–60. Additionally, the patentee did not clearly disavow any scope of the isolating terms. *See, e.g.*, Ex. 4 at -00013016. Thus, the isolating terms should be given their plain and ordinary meaning. *Thorner*, 669 F.3d at 1365.

Defendants' proposed constructions unjustifiably deviate from the plain meaning and the intrinsic record. For example, contrary to Defendants' proposed constructions, the Patents-in-Suit describe using standard isolation techniques to isolate ***both*** free fetal and maternal DNA from a sample, without "increasing the proportion of free fetal versus maternal nucleic acid obtained."[14] *See* '277 Patent at 89:17–31 (stating that template DNA containing both free fetal and maternal DNA "was isolated using the Qiagen Midi Kit"), 220:33–221:21; '720 Patent at 89:51–54, 211:38–63. Defendants do not contend that their proposed constructions are tethered to actual language in the isolating terms. *See* Ex. 6 at 3–4. Rather, Defendants assert that their constructions incorporate the overall "invention" of the Patents-in-Suit. *Id.* But "[i]t is a bedrock principle of patent law

[14] Natera's proposed construction for the isolating term in the '720 Patent, Claim 1 does not require "increasing the proportion of free fetal versus maternal nucleic acid obtained." That construction—"increasing the proportion of free nucleic acid obtained"—does not indicate what the "free nucleic acid" is compared to, injecting new ambiguity into the claim term.

that the claims of a patent define the invention," not defendants' self-serving interpretation of the invention as a whole. *Phillips*, 415 F.3d at 1312 (internal quotations and citation omitted).

B. Defendants' Proposed Constructions Misinterpret The Inventions Of The Patents-In-Suit.

Moreover, Defendants' proposed constructions rely upon a gross misinterpretation of the inventions of the Patents-in-Suit: that the invention increases the proportion of free fetal nucleic acid relative to that found endogenously. Ex. 6 at 4. As the Patents-in-Suit explain, the novel use of an agent that inhibits cell lysis in the claimed methods reduces maternal cell lysis and dilution of free fetal DNA, resulting in an increase in the percentage of free fetal DNA ***relative to samples that have not been treated with such agents***. *See* '277 Patent at 32:22–39; *see also id.* at 89:11–13 ("the percent of fetal DNA in plasma obtained from a pregnant female was determined both in the ***absence*** and presence ***of inhibitors of cell lysis [e.g. formalin]***"), Table XXI (showing that formalin increases the percentage of free fetal DNA relative to reported values ***not treated with formalin***), 220:2–7 ("Such methods or processes typically result in a substantial increase in the ratio of fetal DNA/maternal DNA . . . [as compared to] the ratio of fetal DNA/maternal DNA found in blood samples ***collected by standard procedures***."), 222:24–43; '720 Patent at 25:27–38, 33:33–46, 89:35–37, 91:34–55, 92:10–26, 289:56–298:5. The prosecution histories also confirm that the addition of the claimed agent "increase[s] the proportion of fetal DNA versus maternal DNA obtained from a sample" relative to samples not treated with such an agent. *See* Ex. 3 at 00012668–69, Ex. 4 at -00013027; *see* Ex. 5 at -00015537, Ex. 13 at -00016665–6666. Thus, Defendants' interpretation conflicts with the intrinsic record and should be rejected.

CONCLUSION

For the foregoing reasons, Ravgen respectfully requests that the Court construe the disputed claim terms as proposed by Ravgen.

Dated: December 15, 2020 By: /s/ *Kerri-Ann Limbeek* (*pro hac vice*)

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that all counsel of record who are deemed to have consented to electronic service are being served with a copy of this document via email on December 15, 2020.

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